CARDIOPULMONARY BYPASS, MYOCARDIAL MANAGEMENT, AND SUPPORT TECHNIQUES

CHRONIC NONPULSATILE BLOOD FLOW. II. HEMODYNAMIC RESPONSES TO PROGRESSIVE EXERCISE IN CALVES WITH CHRONIC NONPULSATILE BIVENTRICULAR BYPASS

Ryuji Tominaga, MD
William Smith, DEng
Alex Massiello, ME
Hiroaki Harasaki, MD, PhD
Leonard A. R. Golding, MD

We investigated the effects of stepwise treadmill exercise on animal (calf) hemodynamic variables during chronic nonpulsatile biventricular bypass with ventricular fibrillation. Seven days was allowed for recovery from the effects of anesthesia and surgery; each animal's natural heart was then fibrillated. The pump flows were maintained at nominal rates of 90, 100, and 120 ml · kg^{-1} · min^{-1} for 1 week each, with the order varying from experiment to experiment. A total of 30 incremental exercise tests were performed on five animals. No significant changes in mean aortic pressure were observed during nonpulsatile perfusion at the three nominal flow rates of nonpulsatile flow either before or during exercise. The systemic vascular resistance decreased significantly during exercise (from 705 ± 22 to 547 ± 81 dyne · sec · cm^{-5}, $p < 0.01$, and from 604 ± 25 to 510 ± 15 dyne · sec · cm^{-5}, $p < 0.05$, at nominal flow rates of 100 and 120 ml · kg^{-1} · min^{-1}, respectively). There were also significant (analysis of variance, Scheffe test, $p < 0.05$) differences in systemic vascular resistance among three nominal flow rates both before and during exercise. These results suggest that the autonomic nerve reflex control of the cardiovascular system in physical exercise was functioning normally in animals with chronic nonpulsatile blood flow. (J THORAC CARDIOVASC SURG 1996;111:857-62)

During exercise, the carotid sinus and aortic arch baroreceptors play an important role in regulating the systemic arterial pressure. Several investigations have demonstrated that the shift from pulsatile to static pressure in the isolated carotid sinus or aortic arch attenuates the baroreflex inhibition of sympathetic nerve activity, with a reflexive decrease in the arterial pressure.[1, 2] One limitation of such studies is the acute nature of the investigations. This institution has shown long-term survival in animals and human beings with nonpulsatile blood flow.[3-7] This study was undertaken to examine whether any abnormal cardiovascular responses to progressive exercise were observed in awake calves with chronic nonpulsatile systemic blood flow, uninfluenced by the effects of surgery and anesthesia.

From the Department of Biomedical Engineering, Research Institute, The Cleveland Clinic Foundation, Cleveland, Ohio.

Supported by the G. Harold and Leila Y. Mathers Charitable Foundation.

Received for publication Feb. 21, 1995; accepted for publication June 7, 1995.

Address for reprints: Ryuji Tominaga, MD, Division of Cardiovascular Surgery, Research Institute of Angiocardiology, Faculty of Medicine, Kyushu University, 3-1-1 Maedashi, Higashi-ku, Fukuoka, 812, Japan.

0022-5223/96 $5.00 + 0 **12/1/66820**

Material and methods

These studies were performed on the same animals used for the investigations reported in the other articles of this series.[8, 9] These were 4-month-old calves weighing 89.8 to 93.6 kg at time of implant. As already detailed, Hemadyne centrifugal blood pumps supplied by the now defunct Hemadyne Division of Medtronic, Inc. (Minneapolis, Minn.) were attached to the cardiovascular system, right ventricle to pulmonary artery and left ventricle to aorta. Both pumps idled at 3 to 5 L/min until the seventh postoperative day, when the natural heart was fibrillated and flow rates of 90, 100, or 120 ml · kg^{-1} · min^{-1} were set for 1 week each in random order. Routinely, the atria in time spontaneously converted to sinus rhythm, although the ventricles never recovered. All animals in this study were managed in compliance with the "Principles of Laboratory Animal Care" formulated by the National

Table I. *Hemodynamic changes during treadmill exercise in calves with a chronic nonpulsatile biventricular bypass; the pump flow rate before exercise was set at 90 ml · kg^{-1} · min^{-1}*

Treadmill speed (mph)	*n*	*RA (mm Hg)*	*PA (mm Hg)*	*LA (mm Hg)*	*Ao (mm Hg)*	*AHR (beats/min)*	*Flow/kg (ml/min)*	*SVR (dynes · sec · cm^{-5})*
0 (before)	10	17.3 ± 1.9	26.6 ± 2.1	13.6 ± 2.5	95.8 ± 4.9	124 ± 5	88.1 ± 0.6	778 ± 42
0.3	10	19.7 ± 1.6*	28.2 ± 1.5	16.1 ± 2.3	97.5 ± 4.4	132 ± 5	88.8 ± 0.9	765 ± 38
0.5	5	19.6 ± 2.1	31.6 ± 2.9	14.8 ± 3.6	96.8 ± 6.2	131 ± 9	90.7 ± 0.8*	741 ± 53
0.7	4	18.8 ± 1.3	32.5 ± 4.1	12.3 ± 2.6	92.5 ± 8.5	126 ± 11	92.1 ± 1.7	688 ± 77
0.9	3	18.3 ± 1.9	37.3 ± 0.9	13.7 ± 3.2	91.7 ± 10.1	136 ± 7	90.5 ± 1.1	693 ± 86
1.1	3	20 ± 2.3	37 ± 2.1*	14.3 ± 4.5	91.7 ± 10.9	135 ± 9	90.4 ± 0.7	677 ± 83
0 (after)	10	16.3 ± 1.2	28 ± 2.4	15.5 ± 1.7	96 ± 5.2	124 ± 4	85.6 ± 1.5	814 ± 36

RA, Right atrial pressure; *PA,* pulmonary pressure; *LA,* left atrial pressure; *Ao,* aortic pressure; *AHR,* atrial heart rate; *Flow/kg,* left pump flow per kilogram; *SVR,* systemic vascular resistance, *mph,* miles per hour.

*$p < 0.05$ versus the pre-exercise value according to the paired t test. Data are mean ± standard error of the mean.

Society for Medical Research and the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources and published by the National Academy of Sciences (NIH Publication No. 8023, revised 1978).

Treadmill exercise study. Thirty exercise studies were done with the Animil treadmill intended for animal experiments (Gullwing, Inc., Sandusky, Ohio). The speed of the treadmill was increased at zero slope from 0.3 to 2.1 mph, with 0.2 mph increments 3 minutes in duration. Left pump flow rates were set as close as possible to the intended nominal level before exercise, and the pump controls were left fixed throughout the exercise test. As a result, actual flows varied by a small amount, as indicated by the data tables, as a result of changing atrial and aortic pressures and the pump pressure-flow relationship at the set speed. Hemodynamic variables were monitored continuously and recorded every 3 minutes. Pump flows were monitored by transit-time ultrasonic flow probes clamped on the pump outflow tubing (Transonic Systems, Inc., Ithaca, N.Y.). Pressures were measured with Bentley Trantec model 800 (Baxter Healthcare Corp., Deerfield, Ill.) or Statham P23b (Gould, Inc., Oxnard, Calif.) transducers connected to saline solution–purged catheters leading to the appropriate anatomic sites. Atrial heart rate was determined with external electrocardiographic leads. Body temperature measurements verified that no febrile calves were tested. The preexercise hemodynamic values were recorded as a control measurement when the animal was standing on the Animil. Exercise studies were done twice a week after ventricular fibrillation was induced. The body weight of the calf was measured as part of each exercise study. Because of the random flow order, there was no significant difference with respect to average test day after operation of the 90, 100 and 120 ml · kg^{-1} · min^{-1} flow data (18.5 ± 1.9, 15.3 ± 1.8, and 14.8 ± 1.4 days).

The data were stored and analyzed with a personal computer. The two-tailed paired t test was used to evaluate statistical significance between the preexercise and postexercise data. Statistical significance in multiple comparisons among independent groups of data, in which an analysis of variance indicated the presence of significant differences, was determined by the Scheffe method.[10] Significance was supposed at a value of $p < 0.05$. All data are reported as mean ± standard error of the mean.

Results

At 90 ml · kg^{-1} · min^{-1} nominal preexercise pump flow with ventricular fibrillation. Table I shows the data at treadmill speeds lower than 1.1 mph because the animals would not maintain treadmill exercise levels higher than 1.3 mph under these conditions. Aortic pressure (Fig. 1) and left atrial pressure showed no significant changes during exercise. A statistically significant ($p < 0.02$) increase in right atrial pressure was observed at a treadmill speed of 0.3 mph. Pulmonary arterial pressure also increased after exercise; however, there was no statistical significance in this increase. The systemic vascular resistance, which was calculated with the mean aortic pressure, right atrial pressure, and pump flow rate, decreased during exercise; again, however, this change was not statistically significant (Fig. 2). The left pump flow rate increased statistically significantly ($p < 0.05$), by a maximum of 0.4 L · kg^{-1} · min^{-1} or about 5%.

At 100 ml · kg^{-1} · min^{-1} nominal preexercise pump flow with ventricular fibrillation. Aortic pressure, left atrial pressure, and pulmonary arterial pressure showed no significant changes after exercise. Right atrial pressure, however, increased significantly during the progressive exercise. Atrial heart rate also increased significantly ($p < 0.01$) at most treadmill speeds compared with preexercise values. Left pump flow increased significantly during exercise, but this increase was only approximately 5% of the preexercise value. The systemic vascular resistance decreased significantly ($p < 0.03$) during exercise compared with the preexercise data; pulmonary vascular resistance also decreased significantly (Table II).

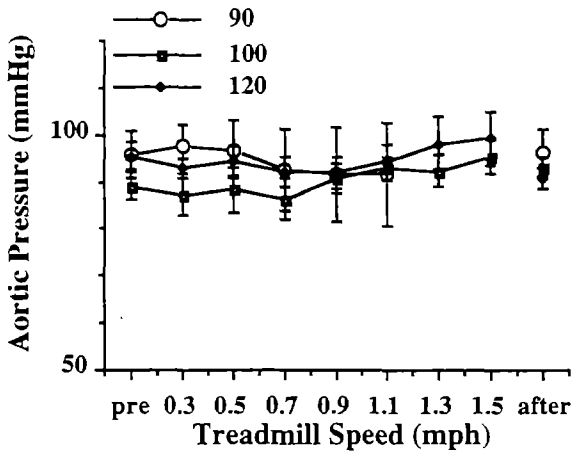

Fig. 1. Aortic pressure changes during treadmill exercise at 90, 100, and 120 ml · kg^{-1} · min^{-1} of nonpulsatile blood flow. *Small bars* indicate standard error of the mean. No statistically significant increases were seen during nonpulsatile blood flow. *pre,* Preexercise value; *after,* 30 minutes after exercise.

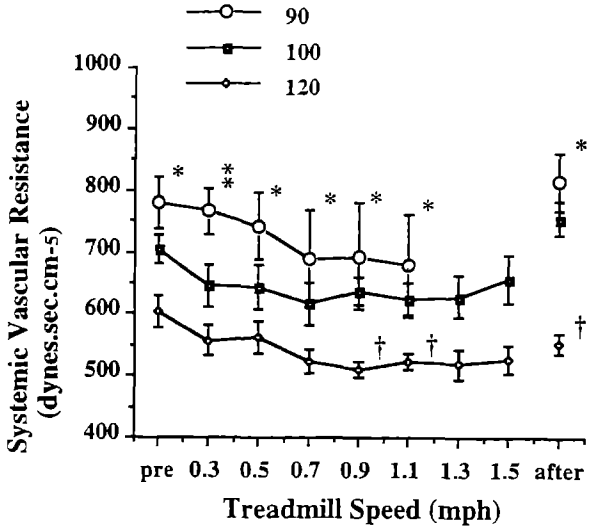

Fig. 2. Changes in systemic vascular resistance values after progressive treadmill exercise. A significant decrease was observed after exercise versus preexercise values at all flow rates (90, 100, and 120 ml · kg^{-1} · min^{-1} of nonpulsatile blood flow). *Small bars* indicate standard error of the mean. *pre,* Preexercise value; *after,* 30 minutes after exercise. Significance set at $p < 0.05$; *asterisk* indicates 90 ml · kg^{-1} · min^{-1} differed from both 100 and 120 ml · kg^{-1} · min^{-1} at all but 0.3 mph, *double asterisk* indicates a difference between 90 and 120 ml · kg^{-1} · min^{-1} at 0.3 mph, and *dagger* indicates a significant difference between 100 and 120 ml · kg^{-1} · min^{-1} at 0.9 mph, 1.1 mph, and after test conditions.

At 120 ml · kg^{-1} · min^{-1} nominal preexercise pump flow with ventricular fibrillation. Aortic pressure did not show any significant changes. Right atrial pressure increased significantly ($p < 0.05$) both during and 30 minutes after exercise. Left atrial pressure increased significantly ($p < 0.05$) only at a speed of 0.3 mph. The atrial heart rate also increased significantly during exercise ($p < 0.05$). The left pump flow again increased, with a small but statistically significant change of approximately 3% of the preexercise value. The systemic vascular resistance decreased significantly during exercise at treadmill speeds of 0.3 mph ($p < 0.05$), 0.7 mph ($p < 0.04$), and 0.9 mph ($p < 0.03$; Table III).

Discussion

A critical role of the circulatory system in exercise is to augment the delivery of metabolic substrate and oxygen necessary to generate adenosine triphosphate and maintain the required level of muscular work. Multiple mechanisms operate to make this happen. During exercise, there is a locally mediated vasodilation in the active muscles, a reflex constriction of the splanchnic and renal vascular beds, and an increase in cardiac output, with each proportional to the workload. An increase in sympathetic nervous activity during dynamic exercise plays a major role in hemodynamic changes.[11]

The details of the autonomic nervous regulation of arterial pressure have been investigated by a number of researchers. Walgenbach and Donald[12] observed an abnormal rise in systemic pressure during and after exercise when both aortic arch denervation and vascular isolation in addition to carotid sinus pressurization were used to interrupt arterial baroreflexes. With carotid baroreceptors alone, the arterial pressure response to exercise was normal. Several other investigators[13, 14] have demonstrated that the shift from pulsatile to steady pressure in the isolated carotid sinus or aortic arch attenuates the baroreflex inhibition of sympathetic nerve activity, resulting in an atypical rise in arterial pressure.

Melcher and Donald[13] showed that dogs without carotid, aortic, or cardiopulmonary baroreceptors became hypotensive and remained hypotensive during mild exercise. During severe exercise, an initial hypotension recovered to the preexercise levels after 90 seconds. McRitchie and colleagues[15] demonstrated the absence of a marked effect of chronically denervated carotid sinus and aortic arch baroreflex afferents on hemodynamic responses to moderate

Table II. *Hemodynamic changes during treadmill exercise in calves with chronic nonpulsatile biventricular bypass at pump flow rate before exercise of 100 ml · kg^{-1} · min^{-1}*

Treadmill speed (mph)	*n*	*RA (mm Hg)*	*PA (mm Hg)*	*LA (mm Hg)*	*Ao (mm Hg)*	*AHR (beats/min)*	*Flow* (ml · kg^{-1} · min^{-1})*	*SVR (dyne · sec · cm^{-5})*
0 (before)	10	10.3 ± 1.3	22.5 ± 2.9	5.9 ± 1.6	89.1 ± 2.9	128 ± 4	101.4 ± 1.2	705 ± 22
0.3	10	13 ± 1.1†	22.6 ± 2.8	7.2 ± 1.3	87.2 ± 4.5	132 ± 5	104.1 ± 1.2‡	646 ± 33‡
0.5	10	13.9 ± 1.3	24.4 ± 3.5	8.3 ± 2.1	88.3 ± 4.9	140 ± 8	104.5 ± 1.6‡	644 ± 35
0.7	10	14.9 ± 1.4	24.4 ± 3.5	8.4 ± 4.3	86.2 ± 4.3	144 ± 8†	104.9 ± 1.5‡	616 ± 24†
0.9	9	16.1 ± 1.5	24.6 ± 3.1	8.6 ± 2.1	90.8 ± 3.3	146 ± 9	105.4 ± 1.8‡	637 ± 22‡
1.1	8	18 ± 1.8	26.7 ± 4.1	11.1 ± 2.2	92.9 ± 2.5	151 ± 10	106.7 ± 1.8‡	647 ± 81†
1.3	7	16.9 ± 1.5	26.3 ± 3.6	9.1 ± 2.1	92.3 ± 3.3	152 ± 10	107.5 ± 2.6	639 ± 32†
1.5	6	16.2 ± 1.8	24.5 ± 3.1	8.7 ± 2.1	95.3 ± 5.5	152 ± 9	107.4 ± 2.4	656 ± 38
0 (after)	10	9.8 ± 1.8	20.9 ± 2.7	6.6 ± 1.3	93.1 ± 2.2	123 ± 4	100.8 ± 2.1	754 ± 28

Data are mean ± standard error of the mean. *RA,* Right atrial pressure; *PA,* pulmonary arterial pressure; *LA,* left atrial pressure; *Ao,* aortic pressure; *AHR,* atrial heart rate; *SVR,* systemic vascular resistance.

*Left pump flow.

†$p < 0.01$ versus preexercise value, according to paired t test.

‡$p < 0.05$ versus preexercise value, according to paired t test.

Table III. *Hemodynamic changes during treadmill exercise in calves with chronic nonpulsatile biventricular bypass at pump flow rate before exercise of 120 ml · kg^{-1} · min^{-1}*

Treadmill speed (mph)	*n*	*RA (mm Hg)*	*PA (mm Hg)*	*LA (mm Hg)*	*Ao (mm Hg)*	*AHR (beats/min)*	*Flow* (ml · kg^{-1} · min^{-1})*	*SVR (dyne · sec · cm^{-5})*
0 (before)	10	13.4 ± 1.7	24.5 ± 2.3	10.1 ± 2.1	95.5 ± 2.8	124 ± 6	120 ± 1.3	604 ± 25
0.3	10	16.8 ± 1.8†	26.7 ± 2.1	11.6 ± 2.2	92.8 ± 2.2	140 ± 7‡	121.8 ± 1.5	557 ± 24§
0.5	10	17.5 ± 1.8†	24.9 ± 1.9	11.6 ± 1.9	94.5 ± 3.2	155 ± 8§	122.1 ± 1.4	562 ± 26
0.7	9	19.3 ± 2.1†	25.7 ± 2.2	12.2 ± 2.1	92 ± 3.2	152 ± 7‡	123.3 ± 1.7‡	522 ± 19§
0.9	7	20.7 ± 2.7†	26.3 ± 2.7	12.9 ± 3.1	91.9 ± 3.5	158 ± 12†	123.6 ± 2.2§	510 ± 15§
1.1	7	20.6 ± 2.5†	26 ± 2.5	13.6 ± 3.1	94.2 ± 3.8	173 ± 14§	124.3 ± 2.3‡	525 ± 15
1.3	6	24.6 ± 3.6†	29.8 ± 3.2	15.3 ± 3.5	98.2 ± 6.3	178 ± 22	123.7 ± 2.9§	518 ± 24
1.5	5	24.2 ± 3.1†	30.8 ± 2.3	17 ± 3.4	99.2 ± 5.8	185 ± 17	123.8 ± 3.3§	526 ± 23
0 (after)	10	16 ± 1.7§	26.4 ± 2.1§	10.5 ± 2.4	90.7 ± 2.4	136 ± 7	121.4 ± 1.6	552 ± 16

Data are mean ± standard error of the mean. *RA,* Right atrial pressure; *PA,* pulmonary arterial pressure; *LA,* left atrial pressure; *Ao,* aortic pressure; *AHR,* atrial heart rate; *SVR,* systemic vascular resistance.

*Left pump flow.

†$p < 0.01$ versus preexercise value, according to paired t test.

‡$p < 0.005$ versus preexercise value, according to paired t test.

§$p < 0.05$ versus preexercise value, according to paired t test.

exercise in dogs. Studies conducted in dogs with and without baroreceptor isolation by Vanhoutte, Lacroix, and Leusen[16] also revealed little difference in the cardiovascular response to exercise.

The experiments reported here show no hypertension at any exercise level and show no hypotension at the initial low intensity level, resembling more the results of McRitchie and associates[15] and Vanhoutte, Lacroix, and Leusen.[16] Apparently, other mechanisms can compensate for the lack of a pulsatile baroreceptor reflex. This is especially significant because the cardiovascular system was triply stressed in this study. The pressure was depulsed; the flow level was very low, even at the highest tested flow level; and the demand response was very low. A left-side perfusion of 90 to 100 ml · kg^{-1} · min^{-1} has already been shown to be minimal for a resting activity level,[7] and the 5% increase in flow is almost inconsequential compared with the 300% or greater potential capacity increase of a normal, healthy heart.[17, 18] The maintenance of normal aortic pressure under these conditions is remarkable.

A moderate increase in aortic pressure is normal during exercise but was not noted here. This may be a result of the very low nominal flow level or of the inability to increase flow with increased demand.[19, 20] Sullivan and coworkers[20] saw a similar effect when comparing the response to exercise of normal subjects and patients with congestive heart failure. It is possible that the high right atrial

pressure triggered a cardiopulmonary reflex that lowered systemic vascular resistance. The effects of the fibrillated natural heart as a neuroendocrine organ are unexplored. The characteristics of the centrifugal pump system, which has a flow-pressure difference relationship quite different from the flow-afterload-preload characteristics of the natural heart or a conventional artificial heart, could also be a factor.

Shoor and colleagues[21] reported the hemodynamic response to exercise in an unanesthetized calf with biventricular centrifugal pumps, but the natural heart was not fibrillated and dominated the hemodynamic profile during exercise. Our research group has reported on exercise studies showing that depulsed animals were capable of exercise and has noted that the results were comparable to those achieved with calves with pulsatile total artificial hearts.[22, 23] This new study adds graded exercise, and selected flow levels to the protocol. At 90 $ml \cdot kg^{-1} \cdot min^{-1}$ perfusion, results are consistent with earlier data. With the 10% increase in flow to 100 $ml \cdot kg^{-1} \cdot min^{-1}$, the animals' ability to tolerate greater intensity of exercise also increased. Curiously, a further 20% increase in flow did not result in performance of yet higher intensity exercise. It appears that the cardiovascular system does not operate in a simple linear manner when apportioning the available blood flow during exercise.

Clinically, these results suggest that even a non-demand-responsive nonpulsatile ventricular-assist system can maintain a patient in a stable, comfortable state at rest and also give the recipient the ability to independently manage tasks such as shaving, dressing, writing, or slow walking. In human applications, the beating heart would not likely be deliberately fibrillated. With the volume overload removed by the assist device, the myocardium might well establish a new compensated state and make a small but useful contribution to the total systemic flow. The atrial heart rate increases seen during this protocol indicate that the drive to the myocardium does increase with exercise under conditions of nonpulsatile flow.

In conclusion, it appears that the cardiovascular system can adjust to nonpulsatile flow, maintaining stable aortic pressures from rest to moderate exercise levels, across a range of perfusion rates. To understand the physiologic mechanisms involved and guide the design of new generations of heart assistance and replacement devices, further studies are warranted at higher flow rates and with demand-responsive nonpulsatile systems, which use information from atrial pressures, atrial heart rate, or venous oxygen content to increase flow output commensurate with workload.

REFERENCES

1. Chapleau MW, Abboud FM. Contrasting effects of static and pulsatile pressure on carotid baroreceptor activity in dogs. Circ Res 1987;61:648-58.
2. Koushanpour E, McGee JP. Effect of mean pressure on carotid sinus baroceptor response to pulsatile pressure. Am J Physiol 1969;216:599-603.
3. Golding LA, Stewart RW, Sinkewich M, Smith W, Cosgrove DM. Nonpulsatile ventricular assist bridging to transplantation. ASAIO Trans 1988;34:476-9.
4. Bolman RM 3rd, Cox JL, Marshall W, et al. Circulatory support with a centrifugal pump as a bridge to cardiac transplantation. Ann Thorac Surg 1989;47:108-12.
5. Golding LR, Murakami G, Harasaki H, et al. Chronic nonpulsatile blood flow. Trans Am Soc Artif Intern Organs 1982;28:81-5.
6. Golding LR, Jacobs G, Murakami T, et al. Chronic nonpulsatile blood flow in an alive, awake animal: 34-day survival. Trans Am Soc Artif Intern Organs 1980;26:251-5.
7. Yada I, Golding LR, Harasaki H, et al. Physiopathological studies of nonpulsatile blood flow in chronic models. Trans Am Soc Artif Intern Organs 1983;29:520-5.
8. Tominaga R, Smith WA, Massiello A, Harasaki H, Golding LA. Chronic nonpulsatile blood flow. I. Cerebral autoregulation in chronic nonpulsatile biventricular bypass and fibrillating heart: carotid blood flow response to hypercapnia. J THORAC CARDIOVASC SURG 1994;108:907-12.
9. Tominaga R, Smith WA, Massiello A, Harasaki H, Golding LAR. Chronic nonpulsatile blood flow. III. Effects of pump flow rate on oxygen transport and utilization in chronic nonpulsatile biventricular bypass. J THORAC CARDIOVASC SURG 1996;111:863-72.
10. Wallenstein S, Zucker CL, Fleiss JL. Some statistical methods useful in circulation research. Circ Res 1980;47:1-9.
11. Smith EE, Guyton AC, Manning RD, White RJ. Integrated mechanisms of cardiovascular response and control during exercise in the normal human. Progr Cardiovasc Dis 1976; 18:421-44.
12. Walgenbach SC, Donald DE. Cardiopulmonary reflexes and arterial pressure during rest and exercise in dogs. Am J Physiol 1983;244:H362-9.
13. Melcher A, Donald DE. Maintained ability of carotid baroreflex to regulate arterial pressure during exercise. Am J Physiol 1981;242:H838-49.
14. Krasney JA, Levitzky MG, Koehler RC. Sinoaortic contribution to the adjustment of systemic resistance in exercising dogs. J Appl Physiol 1974;36:679-85.
15. McRitchie RJ, Vatner SF, Boettcher D, Heyndrickx GR, Patrick TA, Braunwald E. Role of arterial baroreceptors in mediating cardiovascular response to exercise. Am J Physiol 1976;230:85-9.
16. Vanhoutte P, Lacroix E, Leusen I. The cardiovascular adaptation of the dog to muscular exercise: role of the arterial pressoreceptors. Arch Intern Physiol Biochim 1966;74:201-222.
17. Åstrand PO. Quantification of exercise capability and evalu-

ation of physical capacity in man. Progr Cardiovasc Dis 1976;19:51-67.
18. Kremser CB, Rajfer SI. The normal cardiovascular response to exercise. In: Leff AR, ed. Cardiopulmonary exercise testing. Orlando, Florida: Grune & Stratton, 1986.
19. Wilson JR, Martin JL, Schwartz D, Ferraro N. Exercise intolerance in patients with chronic heart failure: role of impaired nutritive flow to skeletal muscle. Circulation 1984; 69:1079-87.
20. Sullivan MJ, Knight JD, Higginbotham MB, Cobb FR. Relation between central and peripheral hemodynamics during exercise in patients with chronic heart failure: muscle blood flow is reduced with maintenance of arterial perfusion pressure. Circulation 1989;80:769-81.
21. Shoor PM, Hammill FS, Griffith LD, Dilley RB, Bernstein EF. Hemodynamic response to exercise in the unanesthetized calf with pulseless arterial flow. Trans Am Soc Artif Intern Organs 1980;26:1-7.
22. Valdes F, Golding LR, Harasaki H, Takatani S, Jacobs G, Nosé Y. Hemodynamic response to exercise during chronic ventricular fibrillation and nonpulsatile biventricular bypass (BVB). Trans Am Soc Artif Intern Organs 1981;27:449-53.
23. Yozu R, Golding LA, Shimomitsu T, et al. Exercise response in chronic nonpulsatile and pulsatile TAH animals. Trans Am Soc Artif Intern Organs 1985;31:22-7.